

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference SCB 815 PCT | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416) | |
| International application No. PCT/EP 03/12375 | International filing date (day/month/year) 06.11.2003 | Priority date (day/month/year) 14.11.2002 |
| International Patent Classification (IPC) or both national classification and IPC C07C201/02 | | |
| Applicant DIPHARMA S.p.A. | | |



1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

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| Date of submission of the demand 25.05.2004 | Date of completion of this report 01.12.2004 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Seelmann, M Telephone No. +49 89 2399-8335  |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/12375**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-9 as originally filed

Claims, Numbers

1-10 filed with telefax on 04.10.2004

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

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5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|------|
| Novelty (N) | Yes: Claims | 1-10 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | 1-10 |
| Industrial applicability (IA) | Yes: Claims | 1-10 |
| | No: Claims | |

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/12375

- D1** WO0110814
D2 WO9825918
D3 K.Treves *et al.*, Environ.Sci.Technol., 34, 1197-1203 (2000)
D4 Kirk-Othmer, Encl. Chem. Technol., 10, 139-139 (1993)

Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Novelty - Art.33(2) PCT

D4 relates to the general knowledge about liquid-liquid extraction in connection with countercurrent performance.

D3 describes the preparation of 1,4-butanediol mononitrate by nitrating 1,4-butanediol with zinc nitrate in presence of DCC and isolation by flash chromatographic work (method 1, page 1198; page 1200, 1st paragraph).

Aliphatic nitroxyalcohols are used in **D1** as starting materials to prepare the corresponding nitroxyalkylesters. In particular, 4-nitroxybutan-1-ol (BDMN) is used in examples 1, 2 and 6 as starting material. These nitroxyalcohols are said in **D1** to be prepared according to the method provided in **D2**. In **D2** the method is outlined based on the preparation of cycloaliphatic nitroxyalcohols by reacting the corresponding diol with nitric acid in chloroform or trichloromethane and performing at the end of the reaction two consecutive extractions, first with water to quench the reaction and then with an organic chlorinated solvent as a second step (preparation 1; preparation 3, stade B; preparation 4, stade B). The final product is purified by chromatographic work. Accordingly the process outlined in **D1/D2** corresponds to example 4 of the present application or the final product obtained after the work-up of the reaction in **D1/D2** is the starting solution/material to be purified in the present application

Accordingly the present purification process is novel.

V.2 Inventive step - Art. 33(3) PCT

The closest purification process of BDMN is known from **D2** and differs in that the nitrate is

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recovered upon chromatographic and not extractive work-up (preparation 1). The technical problem posed is to provide a separation process for BDMN avoiding cristallization and distillation (page 2, lines 8-9). The solution is two successive extractions, first with water followed with a water-immiscible organic solvent. Extraction in two steps has already been performed in **D2** with water and an organic chlorinated solvent to work-up the reaction mixture. Additional extractions in order to purify a product are routine for a skilled person. No inventive step could be recognized for the present process.

Additionally the attention of the applicant is drawn to the fact that performing en extraction in counter-current is commercially the most advantageous one (**D4**, page 137), so that the proposed solution in the dependent claims is obvious in view of **D1/D2** and **D4**.

V.3 Further comments

Certain defects in the international application; Certain observations on the international application

The purification process of the present demand corresponds to an extraction in two steps, first with water: step a), then with a water-immiscible solvent: step b). From the wording of claim 1, the aqueous phase of step a) is to be extracted with the water-immiscible organic solvent of step b). Therefore the reasons for having a dependent claim 5 are confusing. The problem does not reside that there is no support in the description for claim 5. The examiner agrees with the applicant on that point that there is a support for this claim on page 2, lines 24-25. **The present problem is that claims 1 and 5 are identical.** Accordingly claim 5 contravenes to the requirements of conciseness of article 6 PCT, since it repeats what is already provided in claim 1. If the applicant means that additional washings of the aqueous phase are performed in order to extract most of the final product and gathered all the organic phases, then he should have reformulate accordingly ! At the moment this is not what can be understood from the wording of this claim !

CLAIMS

1. A process for the separation of 1,4-butanediol mononitrate from a solution of 1,4-butanediol dinitrate and 1,4-butanediol in a water-immiscible organic solvent, comprising:
 - a) extraction of 1,4-butanediol mononitrate from said solution by water;
 - b) extraction of 1,4-butanediol mononitrate from the resulting aqueous solution, by a water-immiscible organic solvent.
2. A process as claimed in claim 1, characterized in that the extraction according to steps a) and b) is carried out in counter-current in two or more extraction columns.
3. A process as claimed in claim 1, wherein the extraction according to steps a) and b) is carried out in counter-current in 2, 3 or 4 extraction columns.
4. A process as claimed in claim 3, wherein the extraction according to steps a) and b) is carried out in counter-current in 2 extraction columns.
5. A process according to any one of claims 1 - 4 further comprising washing the aqueous phase from step a) with the same water-immiscible organic solvent as that used in the subsequent step b).
6. A process according to any one of claims 1 - 4, comprising the extraction of the resulting organic solution from step a) with the aqueous phase from step b) and the recycle of the aqueous solution to the extraction column of step a).
7. A process according to any one of claims 1 - 6, comprising 1 to 4 extraction cycles according to steps a) and b).
8. A process according to any one of claims 1 - 7, wherein the water-immiscible organic solvent is an organic chlorinated solvent.
9. A process as claimed in claim 3, wherein the chlorinated solvent is

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selected from the group consisting of dichloromethane, trichloromethane, tetrachloromethane, trichloroethane and tetrachloroethane.

10. A process as claimed in claim 9, wherein the chlorinated solvent is dichloromethane.

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